of record. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

STATUS OF THE APPLICATION

Claims 1-46 and 93-101 are pending with entry of this amendment, claims 99-101 being added herein. The amendments introduce no new matter. Support for the amendments, which are made to clarify the claims is replete throughout the specification and claims as filed. That is, the amendments are made largely to make the nomenclature with respect to the use of the term "character strings" more consistent, thereby clarifying where the amended methods relate to sequences (character strings) rather than to actual biopolymers (e.g., nucleic acids or polypeptides). The term character string is used throughout the specification to denote sequences (including, e.g., both regular and encrypted sequences) and to denote correspondence to various biopolymers. The amendments are not made for reasons of patentability, but, as noted, are made to clarify and expand the claims. New claim 99 is fully supported by the specification and claims as filed, e.g., starting at page 39.

The claims were rejected for alleged indefiniteness and for alleged obviousness over Zhao et al. Nature Biotechnology 16:258-261 and Zhao et al. in combination with additional references. Applicants traverse the rejections to the extent that they may be applied to the amended claims.

OBJECTIONS TO THE SPECIFICATION

The Action noted that the specification was not in compliance with MPEP 608.01(b), in that it included browser-executable text. The relevant sections have been amended to make the various internet citations non-browser executable. Accordingly, the objection should be withdrawn.

35 U.S.C. §112, SECOND PARAGRAPH REJECITONS

Claims 8-11, 17, 19, 36 and 93-98 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to various errors in antecedence. Specifically, the phrase "the two or more nucleic acids" was objected to for lack of antecedence in claims 8-11. The phrase has been deleted from the claims, rendering the rejection is moot. Claim 11 was also rejected for lack of

antecedence with respect to claim 1 for use of the term "parental nucleic acid." Claim 1 has been amended for clarity, overcoming the rejection.

Claims 17 and 19 were rejected for lack of antecedence for use of the term "double stranded nucleic acids." The claims have been amended to correct antecedence of claims 17 and 19 to claim 16 (rather than 15) and for clarity in using the term "extended" to more clearly refer to the nucleic acid at issue in claim 16.

Claim 36 was rejected for various typographical errors, as helpfully noted by the Examiner, that have been corrected by amendment. In addition, the commonly used abbreviations for the various proteins have been spelled out as requested by the Examiner.

Claim 93 was rejected for lack of clarity between the preamble and the final method step ("nucleic acid" vs. "nucleic acids"). The claim has been amended to conform the preamble and the final method step more closely to one another.

Each of the clarity issues raised by the Examiner has been addressed as noted above. Accordingly, the rejection should be withdrawn.

AS AMENDED CLAIMS 1-4, 6-9, 12-29, 31-38 AND 40-46 ARE NOT OBVIOUS

Claims 1-4, 6-9, 12-29, 31-38 and 40-46 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Zhao et al. To the extent that the rejection may be applied to the amended claims, Applicants traverse.

As discussed with the Examiner in the helpful Examiner's Interview of August 8, 2001, the claims at issued are easily distinguishable over the staggered PCR procedure of Zhao et al. Specifically, claim 1 relates to a specific procedure in which more than one subsequences is identified in each of at least two different parental sequences. Oligos corresponding to these subsequences are made, annealed to each other and elongated. Thus, at least 4 different oligos are made (at least two per parental sequence) annealed to each other and elongated in the claimed process.

In contrast, Zhao relates to a procedure in which single oligonucleotides are annealed to a template (rather than to each other) and elongated on the template using staggered PCR extension (StEP, *see*, Figure 1). There is no alignment of parental sequences to identify subsequences prior to oligonucleotide synthesis, only one oligonucleotide is synthesized per

template (rather than at least 2), and oligonucleotides are annealed to a template rather than to each other. The procedures of Zhao et al. are essentially unrelated to the claimed methods.

Given that Zhao does not teach the steps of the methods at issue, the reference does not serve as a basis for establishing a *prima facie* case of obviousness. Accordingly, the rejection should be withdrawn.

AS AMENDED CLAIMS 1-29, 31-38 40-46 AND 93-98 ARE NOT OBVIOUS

Claims 1-29, 31-38 40-46 and 93-98 were rejected over Zhao et al. in combination with Venkatsubramanian and further in view of Street. Applicants traverse.

As noted above, Zhao et al. simply does not teach the fundamental steps of the methods at issue. Nothing in Venkatsubramanian or Street remedies these deficiencies.

Furthermore, no *particular* motivation is drawn from the references or the art generally for making the proposed combination of references. That is, there is no articulated reason why one of skill would have attempted to combine the various computer modeling approaches of Venkatsubramanian or Street with Zhao et al.

Zhao et al relates to an essentially random physical process, while Venkatsubramanian and Street relate to approaches which involve modeling and design of molecules to avoid the need for such random physical processes. For example, the process described by Venkatsubramanian involves an in silico method of optimizing molecule sets, followed, presumably, by synthesis and testing of the theoretically optimized molecules. There is no articulated reason why one would take the theoretically optimal molecules and then perform some (unspecified) random physical operation on them. Indeed, given the complete discontinuity between the underlying chemistry of Venkatsubramanian and Zhao et al. (i.e., Venkatsubramanian relates to organic chemical polymers rather than biological nucleic acids), there is no articulated or clear way that the procedures even could be combined.

Because the references do not teach the limitations of the claims and because there could have been no reason to combine the references in the manner suggested, this rejection should also be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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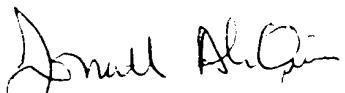
Respectfully submitted,



Jonathan Alan Quine
Reg. No: 41,261

APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/539,486 WITH ENTRY OF THIS AMENDMENT

1 (AMENDED). A method of making a recombinant nucleic acid, the method comprising:

providing a plurality of parental character strings corresponding to a plurality of parental nucleic acids or to a plurality of parental polypeptides, which character strings, when aligned for maximum identity, comprise at least one region of heterology;

aligning the character strings;

defining a set of character string subsequences, which set of subsequences comprises a plurality of subsequences of each of at least two of the plurality of parental character strings;

providing a set of oligonucleotides corresponding to the set of character string subsequences;

annealing the set of oligonucleotides to each other; and,

elongating one or more members of the set of oligonucleotides with a polymerase, or ligating at least two members of the set of oligonucleotides with a ligase, thereby producing one or more recombinant nucleic acid.

2 (AMENDED). The method of claim 1, wherein the character strings, when aligned for maximum identity, comprise at least one region of similarity.

3. The method of claim 1, wherein at least one of the parental character strings is an evolutionary or artificial intermediate.

4 (AMENDED). The method of claim 1, wherein at least one of the parental character strings corresponds to a designed nucleic acid or designed polypeptide.

5. The method of claim 4, wherein the designed nucleic acid represents an energy minimized design for an encoded polypeptide.

6 (AMENDED). The method of claim 1, further comprising applying one or more genetic operator to one or more of the parental character strings, or to one or more of the character string subsequences, wherein the genetic operator is selected from the group consisting of: a mutation of the one or more parental character strings or one or more character string subsequences, a multiplication of the one or more parental character strings or one or more character string subsequences, a fragmentation of the one or more parental character strings or one or more character string subsequences, a crossover between any of the one or more parental character strings or one or more character string subsequences or an additional character string, a ligation of the one or more parental character strings or one or more character string subsequences, an elitism calculation, a calculation of sequence homology or sequence similarity of aligned strings, a recursive use of one or more genetic operator for evolution of character strings, application of a randomness operator to the one or more parental character strings or the one or more character string subsequences, a deletion mutation of the one or more parental character strings or one or more character string subsequences, an insertion mutation into the one or more parental character strings or one or more of character string subsequences, subtraction of the of the one or more parental character strings or one or more character string subsequences with an inactive sequence, selection of the of the one or more parental character strings or one or more character string subsequences with an active sequence, and death of the one or more parental character strings or one or more of character string subsequences.

7 (AMENDED). The method of claim 1, further comprising [selecting] generating a diplomat sequence, which diplomat sequence comprises an intermediate level of sequence similarity between two or more additional members of the plurality of parental character strings wherein the set of oligonucleotides comprises or encodes subsequences of the diplomat sequence.

8 (AMENDED). The method of claim 1, further comprising selecting one or more cross-over sites between the two or more parental character strings and providing the set of oligonucleotides to comprise one or more [corresponding] bridging oligonucleotides [to facilitate recombination between the two or more parental nucleic acids].

9 (AMENDED). The method of claim 8, wherein the two or more parental character strings display low sequence similarity.

10 (TWICE AMENDED). The method of claim 8, further comprising determining a sequence for one or more putative recombinant nucleic acid[s] or polypeptide resulting from in silico recombination of the two or more parental character strings at the cross-over sites, and performing one or more in silico simulation of activity for one or more of the putative recombinant nucleic acid[s] or [for a protein encoded by one or more of the putative recombinant nucleic acids] polypeptide.

11. The method of claim 10, further comprising synthesizing the putative recombinant nucleic acid by providing fragments of the two or more parental nucleic acids and at least one of the corresponding bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

12. The method of claim 1, wherein the set of oligonucleotides comprise a plurality of overlapping oligonucleotides.

13. The method of claim 1, wherein the set of character string subsequences is defined by selecting a length for the character string and subdividing at least two of the plurality of parental character strings into segments of the selected length.

14. The method of claim 1, wherein aligning the character strings is performed in a digital computer or in a web-based system.

15. The method of claim 1, further comprising synthesizing a set of single-stranded oligonucleotides which correspond to the set of character string subsequences, thereby providing the set of oligonucleotides.

16. The method of claim 1, further comprising:

pooling all or part of the set of oligonucleotides;

hybridizing the resulting pooled oligonucleotides; and,

extending a plurality of the resulting hybridized oligonucleotides, wherein at least one of the resulting extended double stranded nucleic acids comprises sequences from at least two of the plurality of parental character strings.

17 (AMENDED). The method of claim [15] 16, further comprising denaturing the extended double stranded nucleic acids, thereby producing a heterogeneous mixture of single-stranded nucleic acids.

18. The method of claim [15] 16, further comprising:

(i) denaturing the extended double stranded nucleic acids, thereby producing a heterogeneous mixture of single-stranded nucleic acids;

(ii) re-hybridizing the heterogeneous mixture of single-stranded nucleic acids; and

(iii) extending the resulting rehybridized double stranded nucleic acids with a polymerase.

19. The method of claim 17, further comprising repeating steps (i) (ii) and (iii) at least twice.

20. The method of claim 1, further comprising selecting the one or more recombinant nucleic acid for a desired property.

21. (AMENDED). The method of claim 1, wherein the set of oligonucleotides is provided by synthesizing the oligonucleotides to comprise one or more modified parental character string subsequence, which subsequence comprises one or more of:

a parental character string subsequence modified by one or more replacement of one or more character of the parental character string subsequence with one or more different character;

a parental character string subsequence modified by one or more deletion or insertion of one or more characters of the parental character string subsequence;

a parental character string subsequence modified by inclusion of a degenerate sequence character at one or more randomly or non-randomly selected positions;

a parental character string subsequence modified by inclusion of a character string from a different character string from a second parental character string subsequence at one or more position;

a parental character string subsequence which is biased based upon its frequency in a selected library of nucleic acids; and,

a parental character string subsequence which comprises, or encodes a polypeptide that comprises, one or more sequence motif, which sequence motif is artificially included in the subsequence.

22. The method of claim 21, wherein the sequence motif comprises an N-linked glycosylation sequence, an O-linked glycosylation sequence, a protease sensitive sequence, a collagenase sensitive sequence, a Rho-dependent transcriptional termination sequence, an RNA secondary structure sequence that affects the efficiency of transcription, an RNA secondary structure sequence that affects the efficiency of translation, a transcriptional enhancer sequence, a transcriptional promoter sequence, or a transcriptional silencing sequence.

23. The method of claim 1, wherein the oligonucleotide set contains one or more altered or degenerate positions as compared to the corresponding subsequence of one or more parental character string.

24. The method of claim 1, further comprising selecting the one or more recombinant nucleic acid based upon its hybridization to a selected nucleic acid or to a set of selected nucleic acids.

25. (AMENDED). The method of claim 1, wherein the plurality of parental character strings comprises at least two parental character strings, wherein the oligonucleotide set comprises at least one oligonucleotide member comprising a chimeric nucleic acid sequence that comprises a subsequence from each of at least two parental character strings, wherein the subsequences from each parental character string are separated by a crossover point.

26. (AMENDED). The method of claim 25, wherein the crossover point is selected by aligning at least one substring of each of at least two of the parental character strings to display pairwise identity between the substrings, and selecting a point within the aligned sequence as the crossover point.

27. The method of claim 25, wherein the crossover point is selected randomly.

28. The method of claim 25, wherein the crossover point is selected non randomly.

29. The method of claim 25, wherein the crossover point is selected non randomly by selecting a crossover point approximately in the middle of one or more identified pairwise identity region.

30. The method of claim 25, wherein at least one crossover point for at least one oligonucleotide member is selected from a region outside of an identified pairwise homology region.

31. The method of claim 1, further comprising adding one or more oligonucleotide member of the set of oligonucleotides at a concentration which is higher than at least one or more additional oligonucleotide member of the set of oligonucleotides.

32. The method of claim 1, further comprising incubating one or more member of the oligonucleotide set with the recombinant nucleic acid and a polymerase.

33. The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid from the oligonucleotide set.

34. (AMENDED). The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid produced by cleavage of at least one parental nucleic acid.

35. (AMENDED). The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid produced by cleavage of a parental nucleic acid, which parental nucleic acid is cleaved by one or more of: chemical cleavage, cleavage with a DNAse, and cleavage with a restriction endonuclease.

36. (AMENDED). The method of claim 1, wherein at least one parental nucleic acid encodes [one or more or] a protein[s] selected from: erythropoietin (EPO), insulin, a peptide hormone, a cytokine, epidermal growth factor, fibroblast growth factor, hepatocyte growth factor, insulin-like growth factor, an interferon, an interleukin[s], a keratinocyte growth factor, a leukemia inhibitory factor, oncostatin M, platelet derived erythroid colony stimulating factor (PD-ECSF), Platelet-derived growth factor (PDGF), pleiotropin, stem cell factor (SCF), c-kit ligand, vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor (G-CSF), an oncogene product, a tumor suppressor, a steroid hormone receptor, a plant hormone, a disease resistance gene, an herbicide resistance gene product, a bacterial gene product, a monooxygenase, a protease, a nuclease, and a lipase.

37. The method of claim 1, wherein the set of oligonucleotides comprises one or more oligonucleotide member between about 20 and about 60 nucleotides in length.

38 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid, or a polypeptide encoded by the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant nucleic acid.

39 (AMENDED). The method of claim 38, further comprising recombining the selected recombinant nucleic acid with one or more of: a homolgous nucleic acid, [and] or an oligonucleotide member from the set of oligonucleotides.

40 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant

nucleic acid, wherein the desired trait or property is selected for in an in vivo selection assay or a parallel solid phase assay.

41 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant nucleic acid, wherein the desired trait or property is selected for in an in vitro selection assay.

42. The method of claim 1, further comprising deconvolution of the recombinant nucleic acid.

43. The method of claim 1, further comprising sequencing or cloning the recombinant nucleic acid.

44. The method of claim 1, wherein the recombinant nucleic acid is synthesized in vitro by assembly PCR.

45. The method of claim 1, wherein the recombinant nucleic acid is synthesized in vitro by error-prone assembly PCR.

46 (AMENDED). The method of claim 1, wherein the parental character strings, or oligonucleotide sets are [selected] provided in a computer.

47-92 are withdrawn

93. (AMENDED). A method of producing one or more recombinant nucleic acids, the method comprising:

providing [sequences of] initial character strings which represent two or more parental nucleic acids or parental polypeptides;

selecting cross-over sites for recombination between the [sequences of the two or more parental nucleic acids] initial character strings, thereby defining [sequences of one or more

recombinant nucleic acids] recombinant character strings that result from a cross-over between [at least two of the sequences of the parental nucleic acids] the character strings;

selecting a sequence of at least one [recombinant nucleic acid] of the recombinant character strings in silico for one or more expected activity of one or more corresponding recombinant nucleic acids or recombinant polypeptides; and,

synthesizing [a] the one or more recombinant nucleic acids or recombinant polypeptides corresponding to one or more of the selected recombinant [sequence] character strings.

94 (AMENDED). The method of claim 93, further comprising [selecting] providing bridging oligonucleotides which correspond to the cross-over sites.

95. (TWICE AMENDED). The method of claim 94, wherein synthesizing the recombinant nucleic acid comprises providing fragments of two or more of the parental nucleic acids and at least one of the corresponding bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

96. (TWICE AMENDED). The method of claim 93, wherein the [sequences of the two or more parental nucleic acids] initial character strings display low sequence similarity.

97. (AMENDED). The method of claim 93, wherein selecting the sequence [of at least one recombinant nucleic acid] of at least one of the recombinant character strings in silico comprises one or more of:

(i) performing an energy minimization analysis of a protein encoded by the [selected recombinant sequence] recombinant character strings;

(ii) performing a stability analysis of at least one protein encoded by the [selected recombinant sequence] recombinant character strings;

(iii) comparing an energy minimized model of at least one protein encoded by the [selected recombinant sequence] recombinant character strings to an energy minimized model of a protein encoded by [one or more of the parental nucleic acids] the initial character strings;

(iv) performing protein threading on one or more protein encoded by the [selected recombinant sequence] recombinant character strings, or [one or more of the parental nucleic acids] the initial character strings; and,

(v) selecting the cross-over sites for recombination between the initial character strings [sequences of two or more parental nucleic acids] to occur within regions of structural overlap of the parental nucleic acids or polypeptides;

(vi) performing one or more of: PDA, a branch-and-terminate combinatorial optimization analysis, a dead end elimination, a genetic or mean-field analysis, or an analysis of protein folding by threading, of the [selected recombinant sequence] recombinant character strings or of a [protein encoded by the selected recombinant sequence] nucleic acid or polypeptide represented by the recombinant character strings;

(vii) performing PDA of at least one initial character string which represents the parental polypeptide or a protein encoded by at least one of the parental nucleic acids; or

(vii) comparing a PDA model of a protein encoded by the [selected recombinant sequence] recombinant character strings to a PDA model of the parental polypeptide or a protein encoded by at least one of the two or more parental nucleic acids.

98 (AMENDED). The method of claim 93, wherein the step of selecting cross-over sites for recombination between the initial character strings [two or more parental nucleic acid sequences] and the step of selecting the at least one recombinant character string [sequence] in silico are performed simultaneously.

PLEASE ENTER THE FOLLOWING NEW CLAIMS

99. The method of claim 1, wherein one or more of the parental character strings comprises a diplomat sequence.

100. The method of claim 8, wherein the two or more parental sequences are less than 50% similar.

101. The method of claim 93, wherein the two or more parental sequences are less than 50% similar.

APPENDIX B

CLAIMS PENDING IN USSN 09/539,486 WITH ENTRY OF THIS AMENDMENT

1 (AMENDED). A method of making a recombinant nucleic acid, the method comprising:

providing a plurality of parental character strings corresponding to a plurality of parental nucleic acids or to a plurality of parental polypeptides, which character strings, when aligned for maximum identity, comprise at least one region of heterology;

aligning the character strings;

defining a set of character string subsequences, which set of subsequences comprises a plurality of subsequences of each of at least two of the plurality of parental character strings;

providing a set of oligonucleotides corresponding to the set of character string subsequences;

annealing the set of oligonucleotides to each other; and,

elongating one or more members of the set of oligonucleotides with a polymerase, or ligating at least two members of the set of oligonucleotides with a ligase, thereby producing one or more recombinant nucleic acid.

2 (AMENDED). The method of claim 1, wherein the character strings, when aligned for maximum identity, comprise at least one region of similarity.

3. The method of claim 1, wherein at least one of the parental character strings is an evolutionary or artificial intermediate.

4 (AMENDED). The method of claim 1, wherein at least one of the parental character strings corresponds to a designed nucleic acid or designed polypeptide.

5. The method of claim 4, wherein the designed nucleic acid represents an energy minimized design for an encoded polypeptide.

6 (AMENDED). The method of claim 1, further comprising applying one or more genetic operator to one or more of the parental character strings, or to one or more of the character string subsequences, wherein the genetic operator is selected from the group consisting of: a mutation of the one or more parental character strings or one or more character string subsequences, a multiplication of the one or more parental character strings or one or more character string subsequences, a fragmentation of the one or more parental character strings or one or more character string subsequences, a crossover between any of the one or more parental character strings or one or more character string subsequences or an additional character string, a ligation of the one or more parental character strings or one or more character string subsequences, an elitism calculation, a calculation of sequence homology or sequence similarity of aligned strings, a recursive use of one or more genetic operator for evolution of character strings, application of a randomness operator to the one or more parental character strings or the one or more character string subsequences, a deletion mutation of the one or more parental character strings or one or more character string subsequences, an insertion mutation into the one or more parental character strings or one or more of character string subsequences, subtraction of the of the one or more parental character strings or one or more character string subsequences with an inactive sequence, selection of the of the one or more parental character strings or one or more character string subsequences with an active sequence, and death of the one or more parental character strings or one or more of character string subsequences.

7 (AMENDED). The method of claim 1, further comprising generating a diplomat sequence, which diplomat sequence comprises an intermediate level of sequence similarity between two or more additional members of the plurality of parental character strings wherein the set of oligonucleotides comprises or encodes subsequences of the diplomat sequence.

8 (AMENDED). The method of claim 1, further comprising selecting one or more cross-over sites between the two or more parental character strings and providing the set of oligonucleotides to comprise one or more bridging oligonucleotides.

9 (AMENDED). The method of claim 8, wherein the two or more parental character strings display low sequence similarity.

10 (TWICE AMENDED). The method of claim 8, further comprising determining a sequence for one or more putative recombinant nucleic acid or polypeptide resulting from in silico recombination of the two or more parental character strings at the cross-over sites, and performing one or more in silico simulation of activity for one or more of the putative recombinant nucleic acid or polypeptide.

11. The method of claim 10, further comprising synthesizing the putative recombinant nucleic acid by providing fragments of the two or more parental nucleic acids and at least one of the corresponding bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

12. The method of claim 1, wherein the set of oligonucleotides comprise a plurality of overlapping oligonucleotides.

13. The method of claim 1, wherein the set of character string subsequences is defined by selecting a length for the character string and subdividing at least two of the plurality of parental character strings into segments of the selected length.

14. The method of claim 1, wherein aligning the character strings is performed in a digital computer or in a web-based system.

15. The method of claim 1, further comprising synthesizing a set of single-stranded oligonucleotides which correspond to the set of character string subsequences, thereby providing the set of oligonucleotides.

16. The method of claim 1, further comprising:

pooling all or part of the set of oligonucleotides;

hybridizing the resulting pooled oligonucleotides; and,

extending a plurality of the resulting hybridized oligonucleotides, wherein at least one of the resulting extended double stranded nucleic acids comprises sequences from at least two of the plurality of parental character strings.

17 (AMENDED). The method of claim 16, further comprising denaturing the extended double stranded nucleic acids, thereby producing a heterogeneous mixture of single-stranded nucleic acids.

18. The method of claim 16, further comprising:

(i) denaturing the extended double stranded nucleic acids, thereby producing a heterogeneous mixture of single-stranded nucleic acids;

(ii) re-hybridizing the heterogeneous mixture of single-stranded nucleic acids; and

(iii) extending the resulting rehybridized double stranded nucleic acids with a polymerase.

19. The method of claim 17, further comprising repeating steps (i) (ii) and (iii) at least twice.

20. The method of claim 1, further comprising selecting the one or more recombinant nucleic acid for a desired property.

21. (AMENDED). The method of claim 1, wherein the set of oligonucleotides is provided by synthesizing the oligonucleotides to comprise one or more modified parental character string subsequence, which subsequence comprises one or more of:

a parental character string subsequence modified by one or more replacement of one or more character of the parental character string subsequence with one or more different character;

a parental character string subsequence modified by one or more deletion or insertion of one or more characters of the parental character string subsequence;

a parental character string subsequence modified by inclusion of a degenerate sequence character at one or more randomly or non-randomly selected positions;

a parental character string subsequence modified by inclusion of a character string from a different character string from a second parental character string subsequence at one or more position;

a parental character string subsequence which is biased based upon its frequency in a selected library of nucleic acids; and,

a parental character string subsequence which comprises, or encodes a polypeptide that comprises, one or more sequence motif, which sequence motif is artificially included in the subsequence.

22. The method of claim 21, wherein the sequence motif comprises an N-linked glycosylation sequence, an O-linked glycosylation sequence, a protease sensitive sequence, a collagenase sensitive sequence, a Rho-dependent transcriptional termination sequence, an RNA secondary structure sequence that affects the efficiency of transcription, an RNA secondary structure sequence that affects the efficiency of translation, a transcriptional enhancer sequence, a transcriptional promoter sequence, or a transcriptional silencing sequence.

23. The method of claim 1, wherein the oligonucleotide set contains one or more altered or degenerate positions as compared to the corresponding subsequence of one or more parental character string.

24. The method of claim 1, further comprising selecting the one or more recombinant nucleic acid based upon its hybridization to a selected nucleic acid or to a set of selected nucleic acids.

25. (AMENDED). The method of claim 1, wherein the plurality of parental character strings comprises at least two parental character strings, wherein the oligonucleotide set comprises at least one oligonucleotide member comprising a chimeric nucleic acid sequence that comprises a subsequence from each of at least two parental character strings, wherein the subsequences from each parental character string are separated by a crossover point.

26. (AMENDED). The method of claim 25, wherein the crossover point is selected by aligning at least one substring of each of at least two of the parental character strings to display pairwise identity between the substrings, and selecting a point within the aligned sequence as the crossover point.

27. The method of claim 25, wherein the crossover point is selected randomly.

28. The method of claim 25, wherein the crossover point is selected non randomly.

29. The method of claim 25, wherein the crossover point is selected non randomly by selecting a crossover point approximately in the middle of one or more identified pairwise identity region.

30. The method of claim 25, wherein at least one crossover point for at least one oligonucleotide member is selected from a region outside of an identified pairwise homology region.

31. The method of claim 1, further comprising adding one or more oligonucleotide member of the set of oligonucleotides at a concentration which is higher than at least one or more additional oligonucleotide member of the set of oligonucleotides.

32. The method of claim 1, further comprising incubating one or more member of the oligonucleotide set with the recombinant nucleic acid and a polymerase.

33. The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid from the oligonucleotide set.

34. (AMENDED). The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid produced by cleavage of at least one parental nucleic acid.

35. (AMENDED). The method of claim 1, further comprising denaturing the recombinant nucleic acid, and contacting the recombinant nucleic acid with at least one additional nucleic acid produced by cleavage of a parental nucleic acid, which parental nucleic acid is cleaved by one or more of: chemical cleavage, cleavage with a DNAse, and cleavage with a restriction endonuclease.

36. (AMENDED). The method of claim 1, wherein at least one parental nucleic acid encodes a protein selected from: erythropoietin (EPO), insulin, a peptide hormone, a cytokine, epidermal growth factor, fibroblast growth factor, hepatocyte growth factor, insulin-like growth factor, an interferon, an interleukin, a keratinocyte growth factor, a leukemia inhibitory factor, oncostatin M, platelet derived erythroid colony stimulating factor (PD-ECSF), Platelet-derived growth factor (PDGF), pleiotropin, stem cell factor (SCF), c-kit ligand, vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor (G-CSF), an oncogene product, a tumor suppressor, a steroid hormone receptor, a plant hormone, a disease resistance gene, an herbicide resistance gene product, a bacterial gene product, a monooxygenase, a protease, a nuclease, and a lipase.

37. The method of claim 1, wherein the set of oligonucleotides comprises one or more oligonucleotide member between about 20 and about 60 nucleotides in length.

38 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid, or a polypeptide encoded by the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant nucleic acid.

39 (AMENDED). The method of claim 38, further comprising recombining the selected recombinant nucleic acid with one or more of: a homolgous nucleic acid, or an oligonucleotide member from the set of oligonucleotides.

40 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant nucleic acid, wherein the desired trait or property is selected for in an in vivo selection assay or a parallel solid phase assay.

41 (AMENDED). The method of claim 1, further comprising selecting the recombinant nucleic acid for a desired trait or property, thereby providing a selected recombinant nucleic acid, wherein the desired trait or property is selected for in an in vitro selection assay.

42. The method of claim 1, further comprising deconvolution of the recombinant nucleic acid.

43. The method of claim 1, further comprising sequencing or cloning the recombinant nucleic acid.

44. The method of claim 1, wherein the recombinant nucleic acid is synthesized in vitro by assembly PCR.

45. The method of claim 1, wherein the recombinant nucleic acid is synthesized in vitro by error-prone assembly PCR.

46 (AMENDED). The method of claim 1, wherein the parental character strings, or oligonucleotide sets are provided in a computer.

47-92 are withdrawn

93. (AMENDED). A method of producing one or more recombinant nucleic acids, the method comprising:

providing initial character strings which represent two or more parental nucleic acids or parental polypeptides;

selecting cross-over sites for recombination between the initial character strings, thereby defining recombinant character strings that result from a cross-over between the character strings;

selecting a sequence of at least one of the recombinant character strings in silico for one or more expected activity of one or more corresponding recombinant nucleic acids or recombinant polypeptides; and,

synthesizing the one or more recombinant nucleic acids or recombinant polypeptides corresponding to one or more of the selected recombinant character strings.

94 (AMENDED). The method of claim 93, further comprising providing bridging oligonucleotides which correspond to the cross-over sites.

95. (TWICE AMENDED). The method of claim 94, wherein synthesizing the recombinant nucleic acid comprises providing fragments of two or more of the parental nucleic acids and at least one of the corresponding bridge oligonucleotides, hybridizing the fragments and the bridge oligonucleotides and elongating the hybridized fragments with a polymerase or a ligase.

96. (TWICE AMENDED). The method of claim 93, wherein the [sequences of the two or more parental nucleic acids] initial character strings display low sequence similarity.

97. (AMENDED). The method of claim 93, wherein selecting the sequence of at least one of the recombinant character strings in silico comprises one or more of:

(i) performing an energy minimization analysis of a protein encoded by the recombinant character strings;

(ii) performing a stability analysis of at least one protein encoded by the recombinant character strings;

(iii) comparing an energy minimized model of at least one protein encoded by the recombinant character strings to an energy minimized model of a protein encoded by the initial character strings;

(iv) performing protein threading on one or more protein encoded by the recombinant character strings, or the initial character strings; and,

(v) selecting the cross-over sites for recombination between the initial character strings to occur within regions of structural overlap of the parental nucleic acids or polypeptides;

(vi) performing one or more of: PDA, a branch-and-terminate combinatorial optimization analysis, a dead end elimination, a genetic or mean-field analysis, or an analysis of protein folding by threading, of the recombinant character strings or of a nucleic acid or polypeptide represented by the recombinant character strings;

(vii) performing PDA of at least one initial character string which represents the parental polypeptide or a protein encoded by at least one of the parental nucleic acids; or

(vii) comparing a PDA model of a protein encoded by the recombinant character strings to a PDA model of the parental polypeptide or a protein encoded by at least one of the two or more parental nucleic acids.

98 (AMENDED). The method of claim 93, wherein the step of selecting cross-over sites for recombination between the initial character strings and the step of selecting the at least one recombinant character string in silico are performed simultaneously.

99. The method of claim 1, wherein one or more of the parental character strings comprises a diplomat sequence.

100. The method of claim 8, wherein the two or more parental sequences are less than 50% similar.

101. The method of claim 93, wherein the two or more parental sequences are less than 50% similar.

APPENDIX C

"MARKED UP" PARAGRAPHS ILLUSTRATING THE AMENDMENTS MADE TO THE SPECIFICATION OF 09/539,486 WITH ENTRY OF THIS AMENDMENT

Please delete the paragraph beginning at page 9, line 5 and ending at page 9, line 13 and substitute therefor the following new paragraph:

An introduction to genetic algorithms can be found in David E. Goldberg (1989) Genetic Algorithms in Search, Optimization and Machine Learning Addison-Wesley Pub Co; ISBN: 0201157675 and in Timothy Masters (1993) Practical Neural Network Recipes in C++ (Book&Disk edition) Academic Pr; ISBN: 0124790402. A variety of more recent references discuss the use of genetic algorithms used to solve a variety of difficult problems. *See*, e.g., [http://]garage.cse.msu.edu/papers/papers-index.html **(on the world wide web)** and the references cited therein; [http://]gaslab.cs.unr.edu/ **(on the world wide web)** and the references cited therein; [http://www.]aic.nrl.navy.mil/ **(on the world wide web)** and the references cited therein; [http://www.]cs.gmu.edu/research/gag/ **(on the world wide web)** and the references cited therein and [http://www.]cs.gmu.edu/research/gag/pubs.html **(on the world wide web)** and the references cited therein.

Please delete the paragraph beginning at page 16, line 26 and ending at page 17, line 16 and substitute therefor the following new paragraph:

One example algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.*, *J. Mol. Biol.* 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information ([http://www.]ncbi.nlm.nih.gov/, **on the world wide web**). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score

can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

Please delete the paragraph beginning at page 20, line 8 and ending at page 20, line 22 and substitute therefor the following new paragraph:

For example, oligonucleotides *e.g.*, for use in *in vitro* amplification/ gene reconstruction methods, for use as gene probes, or as shuffling targets (e.g., synthetic genes or gene segments) are typically synthesized chemically according to the solid phase phosphoramidite triester method described by Beaucage and Caruthers (1981), *Tetrahedron Letts.*, 22(20):1859-1862, *e.g.*, using an automated synthesizer, as described in Needham-VanDevanter *et al.* (1984) *Nucleic Acids Res.*, 12:6159-6168. Oligonucleotides can also be custom made and ordered from a variety of commercial sources known to persons of skill. There are many commercial providers of oligo synthesis services, and thus this is a broadly accessible technology. Any nucleic acid can be custom ordered from any of a variety of commercial sources, such as The Midland Certified Reagent Company (mcrc@oligos.com), The Great American Gene Company ([http://www.]genco.com, **on the world wide web**), ExpressGen Inc. ([www.]expressgen.com, **on the world wide web**), Operon Technologies Inc. (Alameda, CA) and many others. Similarly, peptides and antibodies can be custom ordered from any of a variety of sources, such as PeptidoGenic (pkim@ccnet.com), HTI Bio-products, inc. ([http://www.]htibio.com, **on the world wide web**), BMA Biomedicals Ltd (U.K.), Bio·Synthesis, Inc., and many others.

Please delete the paragraph beginning at page 41, line 19 and ending at page 41, line 31 and substitute therefor the following new paragraph:

If the assay conditions are then altered in only one parameter, different individuals from the library will be identified as the best performers. Because the screening conditions are very similar, most amino acids are conserved between the two sets of best performers. Comparisons of the sequences (e.g., in silico) of the best enzymes under the two different conditions identifies the sequence differences responsible for the differences in performance. Principal component analysis is a powerful tool to use for identifying sequences conferring a particular property. For example, Partek Incorporated (St. Peters, Missouri; [www.]partek.com, **on the world wide web**) provides software for pattern recognition (e.g., which provide Partek Pro 2000 Pattern Recognition Software) which can be applied to genetic algorithms for multivariate data analysis, interactive visualization, variable selection, neural & statistical modeling. Relationships can be analyzed, e.g., by Principal Components Analysis (PCA) mapped scatterplots and biplots, Multi-Dimensional Scaling (MDS) mapped scatterplots, Star plots, etc.

Please delete the paragraph beginning at page 43, line 24 and ending at page 43, line 35 and substitute therefor the following new paragraph:

For example, neural net approaches can be coupled to genetic algorithm-type programming. for example, NNUGA (Neural Network Using Genetic Algorithms) is an available program ([http://www.]cs.bgu.ac.il/~omri/NNUGA/, **on the world wide web**) which couples neural networks and genetic algorithms. An introduction to neural networks can be found, e.g., in Kevin Gurney (1999) An Introduction to Neural Networks, UCL Press, 1 Gunpowder Square, London EC4A 3DE, UK. and at [http://www.]shef.ac.uk/psychology/gurney/notes/index.html **(on the world wide web)** . Additional useful neural network references include those noted above in regard to genetic algorithms and, e.g., Christopher M. Bishop (1995) Neural Networks for Pattern Recognition Oxford Univ Press; ISBN: 0198538642; Brian D. Ripley, N. L. Hjort (Contributor) (1995) Pattern Recognition and Neural Networks Cambridge Univ Pr (Short); ISBN: 0521460867.

Please delete the paragraph beginning at page 44, line 1 and ending at page 44, line 35 and substitute therefor the following new paragraph:

A protein design cycle, involving cycling between theory and experiment, has led to recent advances in rational protein design. A reductionist approach, in which protein positions are classified by their local environments, has aided development of appropriate energy expressions. Protein design programs can be used to build or modify proteins with any selected set of design criteria. *See*, e.g., [http://www.]mayo.caltech.edu/ **(on the world wide web)**; Gordon and Mayo

(1999) "Branch-and-Terminate: A Combinatorial Optimization Algorithm for Protein Design" Structure with Folding and Design 7(9):1089-1098; Street and Mayo (1999) "Intrinsic ß-sheet Propensities Result from van der Waals Interactions Between Side Chains and the Local Backbone" Proc. Natl. Acad. Sci. USA, 96, 9074-9076; Gordon et al. (1999) "Energy Functions for Protein Design" Current Opinion in Structural Biology 9(4):509-513 Street and Mayo (1999) "Computational Protein Design" Structure with Folding and Design 7(5):R105-R109; Strop and Mayo (1999) "Rubredoxin Variant Folds Without Iron" J. Am. Chem. Soc. 121(11):2341-2345; Gordon and Mayo (1998) "Radical Performance Enhancements for Combinatorial Optimization Algorithms based on the Dead-End Elimination Theorem" J. Comp. Chem 19:1505-1514; Malakauskas and Mayo (1998) "Design, Structure, and Stability of a Hyperthermophilic Protein Variant" Nature Struct. Biol. 5:470. Street and Mayo (1998) "Pairwise Calculation of Protein Solvent-Accessible Surface Areas" Folding & Design 3: 253-258. Dahiyat and Mayo (1997) "De Novo Protein Design: Fully Automated Sequence Selection" Science 278:82-87; Dahiyat and Mayo (1997) "Probing the Role of Packing Specificity in Protein Design" Proc. Natl. Acad. Sci. USA 94:10172-10177; Dahiyat et al. (1997) "Automated Design of the Surface Positions of Protein Helices" Prot. Sci. 6:1333-1337; Dahiyat et al. (1997) "De Novo Protein Design: Towards Fully Automated Sequence Selection" J. Mol. Biol. 273:789-796; and Haney et al. (1997) "Structural basis for thermostability and identification of potential active site residues for adenylate kinases from the archaeal genus *Methanococcus*" Proteins 28(1):117-30. These design methods rely generally on energy expressions to evaluate the quality of different amino acid sequences for target protein structures. In any case, designed or modified proteins or character strings corresponding to proteins can be directly shuffled in silico, or reverse translated and shuffled in silico and/or by physical shuffling. Thus, one aspect of the invention is the coupling of high-throughput rational design and in silico or physical shuffling and screening of genes to produce activities of interest.

Please delete the paragraph beginning at page 44, line 1 and ending at page 44, line 35 and substitute therefor the following new paragraph:

Similarly, molecular dynamic simulations such as those above and, e.g., Ornstein et al. ([http://www.]emsl.pnl.gov:2080/homes/tms/bms.html **(on the world wide web)**; Curr Opin Struct Biol (1999) 9(4):509-13) provide for "rational" enzyme redesign by biomolecular modeling & simulation to find new enzymatic forms that would otherwise have a low probability of evolving biologically. For example, rational redesign of p450 cytochromes and alkane dehalogenase enzymes

are a target of current rational design efforts. Any rationally designed protein (e.g., new p450 homologues or new alkaline dehydrogenase proteins) can be evolved by reverse translation and shuffling against either other designed proteins or against related natural homologous enzymes. Details on p450s can be found in Ortiz de Montellano (ed.) 1995, Cytochrome P450 Structure and Mechanism and Biochemistry, Second Edition Plenum Press (New York and London).

Please delete the paragraph beginning at page 51, line 18 and ending at page 51, line 28 and substitute therefor the following new paragraph:

HMM can be used in other ways as well. Instead of applying the generated profile to identify previously unidentified family members, the HMM profile can be used as a template to generate de novo family members (e.g., intermediate members of a cladistic tree of nucleic acids). For example, the program, HMMER is available ([http://]hmmer.wustl.edu/, **on the world wide web**). This program builds a HMM profile on a defined set of family members. A sub-program, HMMEMIT, reads the profile and constructs de novo sequences based on that. The original purpose of HMMEMIT is to generate positive controls for the search pattern, but the program can be adapted to the present invention by using the output as in silico generated progeny of a HMM profile defined shuffling. According to the present invention, oligonucleotides corresponding to these nucleic acids are generated for recombination, gene reconstruction and screening.

Please delete the paragraph beginning at page 59, line 8 and ending at page 59, line 24 and substitute therefor the following new paragraph:

Typically, PDA starts with a protein backbone structure and designs the amino acid sequence to modify the protein's properties, while maintaining it's three dimensional folding properties. Large numbers of sequences can be manipulated using PDA, allowing for the design of protein structures (sequences, subsequences, etc.). PDA is described in a number of publications, including, e.g., Malakauskas and Mayo (1998) "Design, Structure and Stability of a Hyperthermophilic Protein Variant" Nature Struc. Biol. 5:470; Dahiyat and Mayo (1997) "De Novo Protein Design: Fully Automated Sequence Selection" Science, 278, 82-87. DeGrado, (1997) "Proteins from Scratch" Science, 278:80-81; Dahiyat, Sarisky and Mayo (1997) "De Novo Protein Design: Towards Fully Automated Sequence Selection" J. Mol. Biol. 273:789-796; Dahiyat and Mayo (1997) "Probing the Role of Packing Specificity in Protein Design" Proc. Natl. Acad. Sci. USA, 94:10172-10177; Hellinga (1997) "Rational Protein Design – Combining Theory and Experiment" Proc. Natl. Acad. Sci. USA, 94:10015-10017; Su and Mayo (1997)" Coupling Backbone Flexibility and Amino Acid

Sequence Selection in Protein Design" Prot. Sci. 6:1701-1707; Dahiyat, Gordon and Mayo (1997) "Automated Design of the Surface Positions of Protein Helices" Prot. Sci., 6:1333-1337; Dahiyat and Mayo (1996) "Protein Design Automation" Prot. Sci., 5:895-903. Additional details regarding PDA are available, e.g., at [http://www.]xencor.com/ **(on the world wide web)**.

Please delete the paragraph beginning at page 67, line 4 and ending at page 67, line 12 and substitute therefor the following new paragraph:

Similarly, PRINTS (e.g., Atwood et al., *above*) is a compendium of protein motif fingerprints derived from the OWL composite sequence database. Fingerprints are groups of motifs within sequence alignments whose conserved nature allows them to be used as signatures of family membership. Fingerprints can provide improved diagnostic reliability over single motif methods by virtue of the mutual context provided by motif neighbors. The database is now accessible via the UCL Bioinformatics Server on [http:@ www.]biochem.ucl.ac.uk/bsm/dbbrowser/ **(on the world wide web)**. Atwood et al. describe the database, its compilation and interrogation software, and its Web interface. *See also*, Attwood et al. (1997) "Novel developments with the PRINTS protein fingerprint database" Nucleic Acids Res 25(1):212-7.

Please delete the paragraph beginning at page 74, line 5 and ending at page 74, line 16 and substitute therefor the following new paragraph:

One approach to screening diverse libraries is to use a massively parallel solid-phase procedure to screen cells expressing shuffled nucleic acids, e.g., which encode enzymes for enhanced activity. Massively parallel solid-phase screening apparatus using absorption, fluorescence, or FRET are available. *See*, e.g., United States Patent 5,914,245 to Bylina, et al. (1999); *see also*, [http://www.]kairos-scientific.com/ **(on the world wide web)**; Youvan et al. (1999) "Fluorescence Imaging Micro-Spectrophotometer (FIMS)" Biotechnology et alia<[www].et-al.com **(on the world wide web)** > 1:1-16; Yang et al. (1998) "High Resolution Imaging Microscope (HIRIM)" Biotechnology et alia, <[www.]et-al.com **(on the world wide web)** > 4:1-20; and Youvan et al. (1999) "Calibration of Fluorescence Resonance Energy Transfer in Microscopy Using Genetically Engineered GFP Derivatives on Nickel Chelating Beads" posted at [www.]kairos scientific.com **(on the world wide web)**. Following screening by these techniques, sequences of interest are typically isolated, optionally sequenced and the sequences used as set forth herein to design new sequences for in silico or other shuffling methods.

Please delete the paragraph beginning at page 81, line 15 and ending at page 81, line 27 and substitute therefor the following new paragraph:

Generally the charts are schematics of arrangements for components, and of process decision tree structures. It is apparent that many modifications of this particular arrangement for DEGAGGS, e.g., as set forth herein, can be developed and practiced. Certain quality control modules and links, as well as most of the generic artificial neural network learning components are omitted for clarity, but will be apparent to one of skill. The charts are in a continuous arrangement, each connectable head-to tail. Additional material and implementation of individual GO modules, and many arrangements of GOs in working sequences and trees, as used in GAGGS, are available in various software packages. Suitable references describing exemplar existing software are found, e.g., at [http://www.]aic.nrl.navy.mil/galist/ **(on the world wide web)** and at [http://www.]cs.purdue.edu/coast/archive/clife/FAQ/www/Q20_2.htm **(on the world wide web)** . It will be apparent that many of the decision steps represented in Figs. 1-4 are performed most easily with the assistance of a computer, using one or more software program to facilitate selection/ decision processes.